REMARKS

I. STATUS OF THE CLAIMS

Claims 88-89, 92, 94-99, and 109-117 are presently pending with entry of this Amendment. Claims 100-108 were previously withdrawn. Claim 88 has been amended to specify an interferon β polypeptide variant exhibiting interferon β activity, comprising a variant sequence which differs from the wild-type human interferon β sequence SEQ ID NO:2 in no more than 8 amino acid residues, the variant sequence comprising (a) at least one introduced N-glycosylation site comprising two amino acid substitutions relative to SEQ ID NO:2 selected from the group consisting of Q49N+Q51T/S and F111N+R113T/S, and (b) an amino acid substitution at position –1 relative to at least one of the introduced N-glycosylation site(s). Support for the amendment to claim 88 is provided throughout the specification, including at, *e.g.*, but not limited to, page 17, line 17. No new matter has been added. This amendment to claim 88 is made without prejudice to subsequent renewal; Applicants specifically reserve the right to pursue and/or renew any subject matter eliminated from claim 88 in a continuation and/or divisional application.

II. AMENDMENTS TO THE SPECIFICATION

The specification has been amended to correct a number of inadvertent typographical errors. No new matter has been added by these amendments.

III. REJECTIONS UNDER 35 USC § 112, SECOND PARAGRAPH

Claims 88-89, 92, 94-99, and 109-117 were rejected under 35 USC § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention. Office Action, page 2. The Examiner takes the position that the correlation between the variants (up to 15 amino acid changes in SEQ ID NO:2) and the interferon-β activities is not clear, and it is not clear if the variants will possess all or some of the activities of the wild-type protein. *Id.* Claims 89, 92, 94-99 and 109-117 were rejected insofar as they are dependent on rejected claim 88. *Id.*

This rejection is respectfully traversed for at least the reasons set forth in Applicant's previous response dated October 4, 2005. Furthermore, amended claim 88 specifies an interferon β polypeptide variant exhibiting interferon β activity, comprising a sequence which differs from the wild-type human interferon β sequence SEQ ID NO:2 in no more than 8 amino acid residues, the sequence comprising (a) at least one introduced N-glycosylation site comprising two amino acid substitutions relative to SEQ ID NO:2 selected from the group consisting of Q49N+Q51T/S and F111N+R113T/S, and (b) an amino acid substitution at position –1 relative to at least one of the introduced N-glycosylation site(s). The correlation between such variant sequences having no more than 8 amino acid changes compared to SEQ ID NO:2 and particular introduced N-glycosylation site(s) and IFN-β activity is clear. For at least these reasons and those provided in the response dated October 4, 2005, withdrawal of the rejection is respectfully requested.

IV. REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH

A. The Claims Satisfy the Written Description Requirement.

Claims 88-89, 92, 94-99, and 109-117 were rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter that was not clearly described in the specification for the reasons set forth in pages 3-5 of the Office Action dated April 5, 2005. *Id.*, pages 2-3. Specifically, the Examiner is of the view that the specification does not disclose IFN-β variants with up to 15 amino acid changes (including the two glycosylation sites) with any specific IFN-β activity and there is no correlation between disclosed variants and IFN-β activities. *Id.* at page 3. The Examiner states "[a] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." *Id.* at page 4. Claims 89, 92, 94-99, and 109-117 were rejected insofar as they are dependent on rejected claim 88. *Id.*

This rejection is respectfully traversed for at least the reasons set forth in Applicants' response dated October 4, 2005. As was made clear in Applicants' response of October 4, 2005, the specification clearly provides sufficiently detailed and relevant identifying characteristics of the claimed genus defined by claim 88 submitted with that response. Applicants' arguments are

equally applicable to newly amended claim 88 provided herein. Amended claim 88 particularly describes an interferon β polypeptide variant exhibiting interferon β activity, which comprises a sequence that differs from the wild-type human interferon β sequence SEQ ID NO:2 in no more than 8 amino acid residues and has at least one specific introduced N-glycosylation site comprising two amino acid substitutions relative to SEQ ID NO:2 (i.e., Q49N+Q51T/S and F111N+R113T/S) and an amino acid substitution at position –1 relative to at least one of the introduced N-glycosylation site(s).

As explained in detail in Applicants' previous response, the claims meet the written description requirement elucidated by the Federal Circuit and the USPTO's Written Description Guidelines. None of the previous or newly amended claims recites a biomolecule sequence described only by a functional characteristic without any known or disclosed correlation between that function and the structure of the sequence. On the contrary, Applicants disclose specific chemical structural features commonly possessed by all members of the claimed genus of IFN-β polypeptide variants and methods for making them, provide details of the functional characteristics of such polypeptide variants, disclose a sufficiently specific correlation between the claimed structures and the asserted IFN-β activity, and describe methods one can use to test whether a particular structural sequence has the asserted activity. Based on these teachings, one skilled in the art would have plainly recognized that Applicants were in possession of the claimed polypeptide variants and compositions at the time the application was filed. For at least these reasons and those set forth in Applicants' response dated October 4, 2005, withdrawal of the rejection is respectfully requested.

B. <u>The Claims Are Sufficiently Enabled.</u>

Claims 88-89, 92, 94-99, and 109-117 were rejected under 35 USC § 112, first paragraph, because the specification, while being enabling for an interferon-β variant with substitutions at K19R+K45R+K123R of the wild type protein which has antiviral activity, allegedly does not reasonably provide enablement for all IFN-β variants contemplated for the reasons set forth in the Office Action dated April 5, 2005 at pages 4-8. *Id.*, page 4. The Examiner takes the position that "[a]lthough Applicants have provided several examples in the specification of generating

variants, there is no correlation of IFN-β activity provided" and "it is not clear how multiple amino acid changes (15/166 or 10%) within the polypeptide will affect the activities of the protein." *Id.* at pages 4-5.

This rejection is traversed for at least the reasons provided in Applicants' previous response dated October 4, 2005. Further, Applicants' arguments in the previous response are equally applicable to amended claim 88, which specifies more particularly an IFN-β polypeptide variant exhibiting IFN-β activity comprising a sequence which differs from the wild-type human IFN-β sequence SEQ ID NO:2 in no more than 8 amino acid residues and has at least one introduced N-glycosylation site comprising two amino acid substitutions relative to SEQ ID NO:2 selected from the group consisting of Q49N+Q51T/S and F111N+R113T/S and an amino acid substitution at position –1 relative to at least one of the introduced N-glycosylation site(s).

As explained in detail in the previous response, based upon the detailed teachings of the specification (including the guidance provided in the specification regarding specific IFN-β polypeptide variants possessing the asserted activity and methods for making such IFN-β polypeptide variants having such activity), the particularly defined nature of the invention, the numerous working examples, the state of the art, and the high level of skill in the art at the time the application was filed, one of ordinary skill in the art would have been reasonably able to make and use the polypeptide variants defined by amended claim 88, and claims 89, 92, 94-99, and 109-117 dependent thereon, without undue experimentation. For at least these reasons and those provided in Applicants' response dated October 4, 2005, withdrawal of the rejection is respectfully requested.

V. OBVIOUSNESS-TYPE DOUBLE-PATENTING REJECTION

Claims 88-89, 92, 94-99, and 109 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 2, 10, 17-19, and 22-24 of U.S. Patent No. 6,531,122 [hereinafter "the '122 patent"] in view of Apweiler et al., *Biochim. Biophys. Acta* 1473:4-8 (1999) [hereinafter "Apweiler"]. The Examiner takes the position that:

The instant invention is drawn to IFN-β variants (no more than 15 amino acid changes in SEQ ID NO:2) with at least one introduced N-glycosylation.

Pederson et al. (U.S. Patent No. 6,531,122) disclose IFN-β variants exhibiting IFN-β activity, comprising a variant sequence, which differs from the wild type human IFN-β sequence SEQ ID NO:2 in no more than 15 amino acid residues. However, the claims do not specifically recite N-glycosylation at sites Q49N+Q51T/S and F111N+R113T/S.

Apweiler et al. (1999) disclose the N-glycosylation consensus sequence NXS/T (where X can be any amino acid but proline) required for N-glycosylation of protein. Therefore, it would have been *prima facie* obvious at the time of the invention to generate N-glycosylated IFN-β because Apweiler et al. reference identifies the consensus sequence required for N-glycosylation. One of ordinary skill in the art would have been motivated to generate N-glycosylated because of the stability of the protein. Therefore, the instant invention are [sic] rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 10, 17, 18, 19 and 22-24 of U.S. Patent No. 6,531,122 in view of Apweiler et al. (1999).

This rejection is respectfully traversed as follows. The doctrine of obviousness-type double patenting is a judicially created doctrine designed to prevent improper extension of patent rights by prohibiting the issuance of claims in a second patent that are directed to subject matter that is not patentably distinct from the subject matter of the claims in the prior first patent. To establish a *prima facie* case of obviousness-type double-patenting of a claim pending in a later patent application, such claim must be shown to be patentably indistinct from a claim in an earlier issued patent. The claim of the earlier issued patent must be applied alone or as a primary reference combined with one or more additional references to demonstrate the unpatentability of the claim in the later application. There must be clear evidence to show why the subject matter of a claim in the second later application would have been obvious over the subject matter of a claim in the first issued patent – applied alone or in combination with a reference.

Applicants respectfully submit that a proper *prima face* case of obviousness-type double-patenting has not been established. Prior to the instant amendment, claim 88 specified an interferon β polypeptide variant exhibiting interferon β activity, comprising a variant sequence which differs from the wild-type human interferon β sequence SEQ ID NO:2 in no more than 15 amino acid residues, the sequence comprising (a) at least one introduced N-glycosylation site comprising two amino acid substitutions relative to SEQ ID NO:2 selected from the group consisting of Q49N+Q51T/S and F111N+R113T/S, *and (b) an amino acid substitution at position –1 relative to at least one of the introduced N-glycosylation site(s).* As presently

amended, claim 88 specifies an interferon β polypeptide variant exhibiting interferon β activity, comprising a sequence which differs from the wild-type human interferon β sequence SEQ ID NO:2 in no more than 8 amino acid residues, the sequence comprising (a) at least one introduced N-glycosylation site comprising two amino acid substitutions relative to SEQ ID NO:2 selected from the group consisting of Q49N+Q51T/S and F111N+R113T/S, *and (b) an amino acid substitution at position –1 relative to at least one of the introduced N-glycosylation site(s).*

In either instance, claim 88 particularly specifies that the interferon β polypeptide variant comprises a sequence which differs from the wild-type human interferon β sequence SEQ ID NO:2 by no more than a certain number of amino acid residues and comprises at least one introduced N-glycosylation site comprising substitutions Q49N+Q51T/S or F111N+R113T/S relative to SEQ ID NO:2 **and an amino acid substitution at position –1 relative to at least one of the introduced N-glycosylation site(s)**. The specification specifically explains that glycosylation at a given N-glycosylation site may be increased by modifying an amino acid residue at a position –1 relative to the N-glycosylation site. See the specification, including at, but not limited to, *e.g.*, page 18, line 14 to page 28, line 10. Dependent claim 110, for example, specifies more particularly that the polypeptide variant of claim 88 comprises at least one introduced N-glycosylation site comprising substitutions Q49N+Q51T/S and an amino acid substitution at position -1 relative to this N-glycosylation site selected from the group of Q48F, Q48V, Q48W, and Q48Y. Dependent claim 111 recites more specifically that the polypeptide variant of claim 88 comprises at least one introduced N-glycosylation site comprising substitutions F111N+R113T and an amino acid substitution at position -1 relative to this N-glycosylation site selected from the group of D110F, D110V, D110W, and D110Y.

Applicants respectfully submit that the Examiner has not shown and cannot show that any of claims 88, 89, 92, 94-99, and 109 are unpatentable for obviousness-type double-patenting over any claim of the '122 patent – taken alone or in view of the teachings of Apweiler. None of the claims of the '122 patent recites or suggests an interferon β polypeptide variant comprising a sequence which differs from the wild-type human interferon β sequence SEQ ID NO:2 in no more than 8 amino acid residues and comprises at least one introduced N-glycosylation site comprising two substitutions selected from Q49N+Q51T/S or F111N+R113T/S and an amino

acid substitution at position –1 relative to at least one of the introduced N-glycosylation site(s). The subject matter of each of claims 88, 89, 92, 94-99, and 109 is clearly patentably distinct from the subject matter defined by the claims of the '122 patent.

The teachings of Apweiler do not alter this conclusion, as Apweiler does not remotely teach or suggest making any protein variant of a wild-type protein wherein the sequence of the protein variant comprises, e.g., an introduced N-glycosylation site and an amino acid substitution at a position –1 relative to the introduced N-glycosylation site. Neither claim 88 nor any other claim dependent thereon constitutes an obvious variation of any of claims 1, 2, 10, 17-19, 19, and 22-24 of the '122 patent in combination with the teachings of Apweiler. On the contrary, the subject matter of each of claims 88, 89, 92, 94-99, and 109 is plainly patentably distinct from the subject matter of the claims of the '122 patent in view of Apweiler.

For at least these reasons, Applicants submit that the rejection is improper and respectfully request that it be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 298-5809.

Respectfully submitted,

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February 3, 2006
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